PATENT
Docket No. 2026-4003US3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Waldmann, T.	Group Art Unit: 1642
Serial No.	:	08/478,748	Examiner: P. Gambel
Filed	:	June 7, 1995	
For	:	METHOD FOR TREATING MALIGNANCY AND AUTOIMMUNE DISORDERS IN HUMANS USING ANTI-TAC ANTIBODIES	

CERTIFICATE OF MAILING (37 C.F.R. 1.8(a)

COMMISSIONER FOR PATENTS
Washington, D.C. 20231

Sir:

I hereby certify that the attached 1) Appeal Brief (in triplicate); 2) check in the amount of $310.00; 3) Appeal Brief Transmittal (2 pages) and 4) Return postcard (along with any paper(s) referred to as being attached or enclosed) and this Certificate of Mailing are being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the: Commissioner for Patents, Washington, D.C. 20231.

Respectfully submitted,

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Date: April 27, 2001

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For: METHOD FOR TREATING MALIGNANCY AND AUTOIMMUNE DISORDERS IN HUMANS USING ANTI-TAC ANTIBODIES

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5-8-01

APPEAL BRIEF/REPLY BRIEF/SUPPLEMENTAL BRIEF TRANSMITTAL

Commissioner for Patents
Washington, D.C. 20231

Sir:

☒ Transmitted herewith in triplicate is the Appeal Brief for Appellant(s) which is due on April 28, 2001. The Notice of Appeal was filed on February 28, 2001.

☐ Transmitted herewith in triplicate is the Reply Brief for Appellant(s) which is due on _____. The Examiner's Answer was mailed on _____.

☐ Transmitted herewith in triplicate is a Supplemental Brief for Appellant(s) which is due on _____ in response to the Office Action reopening prosecution on _____. Appellant(s) hereby request that the appeal of the above-identified application be reinstated.

☐ A Petition and Fee for Extension of Time to extend the term for filing the
☐ Appeal Brief ☐ Reply Brief ☐ Supplemental Brief is enclosed.

The item(s) checked below are appropriate:

☒ Appeal Fee (Large Entity) - $310.00

☐ Appeal Fee Under 37 CFR §1.9(f) (Small Entity) - $155.00

☐ Fee enclosed ☐ Fee not required (Fee paid in prior appeal)

☐ Charge fee to Deposit Account No. 13-4500, Order No. _____. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

☒ The Commissioner is hereby authorized to charge any additional fees which may be required by this paper, or credit any overpayment to Deposit Account No. 13-4500, Order No.2026-4003US3. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,

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Dated: April 27, 2001

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicants	:	Waldmann, T.	**Group Art Unit:** 1642
Serial No.	:	08/478,748	**Examiner:** P. Gambel
Filed	:	June 7, 1995	
For	:	METHOD FOR TREATING MALIGNANCY AND AUTOIMMUNE DISORDERS IN HUMANS USING ANTI-TAC ANTIBODIES	

APPEAL BRIEF

Commissioner for Patents
Washington, D.C. 20231

Sir:

Appellants submit this brief in support of their appeal. The appeal is from the decision of the Examiner in the Office Action mailed November 28, 2000, which finally rejected Appellant's Claim 27.

Based on the arguments presented herein, Appellant requests that the Board of Patent Appeals and Interferences order that the final rejection of November 28, 2000 be withdrawn, that Appellant's Claim 27 be confirmed as patentable, and that a certificate be issued confirming patentability.

I. REAL PARTY IN INTEREST

The real party in interest of the patent on appeal is its assignee, Government of the United States of America, as represented by the Secretary of Health and Human Services (referred to herein as the "NIH"). All right, title and interest to the above-identified patent application was assigned by the inventor, Dr.

Thomas A. Waldmann to the NIH in an assignment document, recorded in the Patent and Trademark Office on February 9, 1993 at Reel 6436, Frame 0152.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to the Appellant, the Appellant's legal representative, or assignee that will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

Claim 27 is pending in this application. The application was originally filed with claims 1-25. In an amendment filed December 3, 1996, claims 24 and 25 were amended. In a second amendment filed June 4, 1997, claims 1 and 24 were amended.

A first submission under 37 C.F.R. §129(a) was filed on August 4, 1997. New claim 26 was added, claim 1 was amended and claims 19-23 were cancelled in an amendment filed on March 23, 1998.

A second submission under 37 C.F.R. §129(a) was filed on March 24, 1999. Also on that date, claim 27 was added and claims 1-8 and 24-26 were cancelled. Claim 27 was amended in a response filed September 12, 2000.

Claim 27 has been rejected and is the involved claim in this appeal. A copy of Claim 27 as pending is provided in the attached Appendix.

IV. STATUS OF AMENDMENTS

No amendments have been filed subsequent to the final rejection

mailed on November 28, 2000.

V. SUMMARY OF THE INVENTION

The present invention relates to an immunosuppressive method of treating and eliminating disease-associated Tac-positive cells [Spec., p. 4, l. 16-18]. More specifically, the present invention provides a method of treating T-cell mediated disorders in humans, wherein such disorders include, *inter alia*, adult T-cell leukemia, autoimmune dysfunction or allograft incompatibility. [Spec., p. 4, l. 19-31]. The instant method comprises determining a dosage of ^{90}Y-conjugated anti-Tac-antibody, wherein the dose is 2 mg total anti-Tac if the patient has soluble IL-2R levels of less than 2,000 units/ml, the dose is 5 mg total anti-Tac if the patient has soluble IL-2R levels of 2,000 to 10,000 units/ml, the dose is 10 mg of total anti-Tac if the patient has soluble IL-2R levels of 10,000 to 50,000 units/ml and the dose is 20 mg of total anti-Tac if the patient has soluble IL-2R levels greater than 50,000 units/ml and administering this dosage to humans afflicted with a T-cell mediated disorder [Spec. p. 51, l. 29, p. 52, l. 2].

VI. ISSUES

1. Is claim 27 unpatentable under 35 U.S.C. §102(b) as being anticipated by or, in the alternative, under 35 U.S.C. §103 as obvious over Waldmann (Blood 82: 1701-1712, 1993) ["Waldmann, 1993"], as evidenced by Waldmann et al. (Blood 86:4063-4075, 1995) ["Waldmann, 1995"] and/or Vriesendorp (Int. J. Radiation Oncology 22:37-45, 1991) ["Vriesendorp"]?

2. Is claim 27 unpatentable under 35 U.S.C. §103(a) as being obvious over Waldmann 1993 and/or Waldmann (Important Adv. Oncol., 1994:892) ["the IAO reference"] and/or Waldmann (Leukemia 7, Suppl 2:S151-S156) ["the Leukemia reference"] and/or Waldmann (Ann. Oncol. 5:13-17, 1994) ["the Ann.Oncol. reference"] in view of Vriesendorp and Rubin (Ann. Int. Med. 113:619-627, 1990) ["Rubin"]?

VII. GROUPING OF CLAIMS

Only one claim, claim 27, is at issue.

VIII. ARGUMENT

Issue 1: ***Is claim 27 unpatentable under 35 U.S.C. §102(b) as being anticipated by or, in the alternative, under 35 U.S.C. §103 as obvious over Waldmann (Blood 82: 1701-1712, 1993) ("Waldmann 1993"), as evidenced by Waldmann et al. (Blood 86:4063-4075, 1995)("Waldmann 1995") and/or Vriesendorp (Int. J. Radiation Oncology 22:37-45, 1991)("Vriesendorp")?***

A. The Cited References

1. The Waldmann 1993 Reference

The Waldmann 1993 reference describes the use of *unlabelled* anti-Tac in patients with human adult T-cell leukemia ("ATL"). These patients are described to have a "pretherapy serum soluble IL-2R (sIL-2Rα) levels of 920 to 230,370 U/mL". [*see* page 1703, col. 2, lines 7-8 of "Results" section]. Thus, it describes administering the same dose of unlabeled anti-Tac to patients having varying soluble IL-2R levels. The "initial basic protocol" as described in column 2 on page 1704, states that the anti-Tac therapy "involved the administration of 20 mg

anti-Tac on two occasions during the first week and 40 mg anti-Tac on two occasions during the second week of therapy for each patient (Table 2)". Based upon the results of these initial treatment protocols, the dosages were altered, as described on page 1705, column 2. Here, Waldmann states:

> In light of these early observations, to achieve a rapid saturation of IL-2R, the basic dosing schedule was altered for the final 10 patients in the group so that 50 mg anti-Tac per patient was administered on two occasions during the first week of therapy and on two occasions during the second week of therapy.

Thus, the Waldmann 1993 article teaches that it is preferred to use a 50 mg anti-Tac dose, in order to saturate IL-2R.

2. The Waldmann 1995 Reference

Waldmann 1995, is not prior art to the instant application. This reference was published on December 1, 1995, whereas the instant application was filed on June 7, 1995. Thus, the reference was published after the effective filing date of the instant application, and therefore cannot constitute prior art pursuant to sections 102 or 103 of the Patent Statute.

The Waldmann 1995 reference describes a clinical study of ATL patients using a ^{90}Y-labeled Tac antibody.

3. The Vriesendorp Reference

Vriesendorp describes the use of radiolabeled antiferritin antibodies for radioimmunoglobulin therapy for refractory Hodgkin's disease patients. Vriesendorp describes three different labeling procedures for chelating indium and yttrium. The

first method uses isothiocyanoto-benzyl DTPA (diethylene triamine pentaacetic acid) or "ITCB method" developed by Hybritech, Inc. The second method employs a diester linkage ethylene glycol bis (succinimethyl succinate) was introduced between the antibody and the chelator which is referred to at the "EGS method." The third method is site-specific conjugation to the antibody oligosaccharide moiety as described in reference 16 of Vriesendorp. These conjugation methods produced antibodies with specific activities of "2-5 mCi per mg protein for indium-111 labeled antibodies, and between 5-40 mCi per mg protein for yttrium-90 labeled antibodies." Vriesendorp does not indicate which of the methods were used to chelate yttrium, nor is there any indication as to why there is such a broad range of radioactivity per mg of antibody.

B. The Examiner's Position

The Examiner has finally rejected claim 27 over Waldmann 1993, as evidenced by Waldmann 1995, and/or Vriesendorp as being anticipated and/or obvious. The Examiner has taken the position that Waldmann 1995 and Vriesendorp are provided "to support that the inherency of prior art teaching of 5-15 mCi doses of ^{90}Y anti-Tac antibody ... encompasses the total amount of 2-20 mg anti-Tac encompassed by the claimed methods." Alternatively, the Examiner takes the position that "it would have [been] obvious to give 20 mg of anti-Tac comprising 5-15 mCi Yttrium to patients with sIL-2R levels of greater than 50,000 given the clinical result/duration of the different patients in these studies." The Examiner repeatedly takes the position that "for examination purposes given the claimed

recitation; all that is required of the prior art is to provide a dosage of mCi and an amount of ^{90}Y-conjugated anti-Tac to a patient with one of the soluble IL-2R levels."

The Examiner has focused on two statements in Waldmann 1993. First, on page 1710, col.1, the Examiner asserts that Waldmann 1993 "discloses that using radiolabeled anti-Tac in conjunction with unmodified anti-Tac, only 2-17 mg of infused anti-Tac per patient is required to yield circulating bioavailable anti-Tac that can bind to Tac expressing ATL cells." Second, on page 1711, col. 1, Waldmann 1993 describes "that conjugating anti-Tac with cytotoxic agents, such as 5-15 mCi ^{90}Yttrium, was employed to improve the effectiveness of IL-2R-directed therapy of ATL." Based upon these passages, the Examiner has concluded that "it would be readily apparent to one of ordinary skill in the art at the time the invention was made that the Waldmann et al. (1993) that the claimed 2-20 mg is met by the prior art teaching of treating ATL patients with 5-15 mCi doses of ^{90}Y anti-Tac antibody."

With respect to the Waldmann 1995 reference and the Vriesendorp references, the Examiner takes the position that these references are "provided simply to show an inherent property of the prior art methods." The Examiner rejects the holding of *Continental Can Co., USA, Inc. v. Monsanto Co.* and maintains that the "missing descriptive matter is necessarily present in the thing described in the reference and so recognized by persons of ordinary skill."

C. The Claim at Issue

Claim 27 is directed to a method of reducing levels of Tac-positive cells in patients with elevated levels of Tac-positive cells. This method requires the steps

of determining a dosage and administering the dosage to the patient to eliminate the disease-associated Tac-positive cells. Determining the dosage is an important step in this method and comprises 5-15 mCi ^{90}Y-conjugated anti-Tac in a total amount of 2-20 mg anti-Tac, wherein the dose is 2 mg total anti-Tac if the patient has a soluble IL-2R level of less than 2,000 units/ml, the dose is 5 mg total anti-Tac if the patient has a soluble IL-2R level of between 2,000-10,000 units/ml, the dose is 10 mg of total anti-Tac if the patient has a soluble IL-2R level of 10,000-50,000 units/ml, and the dose is 20 mg of total anti-Tac if said patient has a soluble IL-2R level of greater than 50,000 units/ml.

D. Appellant's Response

Appellant urges that the Examiner's position is in error of both the law as well as the facts. The Examiner has incorrectly applied the Doctrine of Inherency to the Waldmann 1993 reference to reach the present invention. Inherent anticipation cannot be established based upon mere possibilities or probabilities. Further, the claimed invention is not obvious in view of the Waldmann 1993 reference, because one skilled in the art could not have recognized the claimed invention based upon the Waldmann 1993 reference. Factually, the Examiner has distorted the teachings of the Waldmann 1993 reference. These errors have led to the erroneous conclusion of unpatentability.

i. The Examiner's Factual Errors

The Examiner has mischaracterized the teachings of the Waldmann 1993 reference. In this reference, *unlabeled* anti-Tac is administered to patients

having soluble IL-2R levels ranging from 920 to 230,370 U/mL, yet the patients all received the same amount of anti-Tac. Thus, Waldmann 1993 makes no distinction regarding dosage based upon the soluble IL-2R levels in the patients. None of the patients' dosages were based upon the patients' sIL-2R levels and none of the patients in this study received a labeled anti-Tac compound.

Later in the Waldmann 1993 article, Waldmann discusses the use of an indium-labeled anti-Tac to determining the minimum levels of anti-Tac necessary to show "circulating bioavailable" levels of anti-Tac. These levels are in stark contrast to "saturating" levels of anti-Tac which were administered for therapeutic purposes. In describing the dosing schedule, Waldmann states: "Dosing schedules were modified slightly in some patients, and additional 20- or 50-mg doses were administered during subsequent weeks *to maintain the saturation* of the IL-2R with the anti-Tac monoclonal antibody." [Waldmann 1993, at 1702, col. 2]. In the Waldmann 1993 article, the focus for determining dosage is to maintain "saturation" of the soluble IL-2R. Thus, the description in Waldmann 1993 of use of 2-17 mg anti-Tac was not provided to teach a therapeutic amount but rather describes a minimum amount needed to have circulating bioavailable anti-Tac.

Indeed for *therapeutic* purposes, Waldmann 1993 starts the clinical study using 20-50 mg, then *increases* the doses to 50 mg, stating: "In light of these early observations, to achieve a rapid saturation of IL-2R, the basic dosing schedule was altered for the final 10 patients in the group so that 50 mg anti-Tac per patient was administered on two occasions during the first week of therapy and on two

occasions during the second week of therapy." [Waldmann 1993 at 1705]. In fact, Waldmann goes on to emphasize the need for this higher dose by stating: "Additional doses of 50 mg anti-Tac *to maintain receptor saturation* were administered to patients who made an initial partial or complete response to therapy." [*Id.*].

ii. *The Examiner's Error Regarding Inherent Anticipation*

Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient to demonstrate an inherent anticipation. *Hansgirg v. Kemmer*, 102 F.2d 212 (CCPA 1939). Furthermore, anticipation by inherency requires that 1) the missing descriptive matter be "necessarily present" in the prior art reference and that 2) it would be so recognized by persons of ordinary skill in the art. *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed.Cir. 1991).

The Examiner in this case has blatantly applied hindsight in order to assert that the earlier reference inherently discloses the claimed invention. In fact, the Examiner relies on art published after Appellant's filing date to allegedly demonstrate that the earlier reference inherently discloses the claimed invention. In particular, Waldmann 1995, has been cited by the Examiner as "disclos[ing] that the Phase I trials disclosed in the Waldmann, *Blood*, 1993 teaching led to algorithm encompassed by the claimed methods." Based upon this later reference, the Examiner concludes that the dosing is an inherent property of the Phase I studies described in Waldmann 1993. This argument is seriously flawed.

Nothing in the Waldmann 1993 reference teaches or suggests the

dosing determination as claimed. Instead, the reference describes the use of a different dosage, i.e. 20-50 mg of anti-Tac for the treatment of patients. Nothing in the references teaches or suggests the use of anti-Tac at doses less than the 20-50 mg described in the article. In fact, the article suggests that the 50 mg dose is preferred. There is simply no teaching or suggestion to the skilled artisan that (a) the dose should be less than 20 mg (i.e. 2-20 mg, as claimed), or (b) that there is any correlation between the soluble IL-2R levels and the recommended dosage. The position that the naked description of a study using 5-15 mCi of ^{90}Y conjugated anti-Tac *inherently* discloses the dosage determination claimed is incorrect.

The doctrine of inherency is misplaced based upon the present facts. The Examiner has taken a "retrospective view" of the art, that is, the Examiner has applied a reference, published *after* the filing date of the instant application, to teach that which is missing from the prior art. This is a classic case of the improper use of hindsight to reach the instant invention. The Federal Circuit has repeatedly pointed out the improperness of such action. For example, in *In re Newell*, (891 F.2d 899, 901 (Fed. Cir. 1989)), the court stated:

> A retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements of the particular claimed combination. It is well established that in deciding that a novel combination would have been obvious, there must be supporting teaching in the prior art. 'That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.'
> (citations omitted.)

See also Sensonics, Inc. v. Aerosonic Corp., 81 F.3d 1566, 1570 (Fed. Cir. 1996)

("To draw on hindsight knowledge of the patented invention, when the prior art does not contain or suggest that knowledge, is to use the invention as a template for its own reconstruction—an illogical and inappropriate process by which to determine patentability.").

The Examiner asserts that the claim is anticipated by Waldmann 1993, based upon the inherent disclosure of the claimed method. The reference itself does not teach or suggest the claimed method. In fact, as discussed above, the reference specifically teaches the use of unlabeled anti-Tac at doses of 20-50 mg, preferably at the higher dose. In one paragraph, the authors provide a cursory description of a study using yttrium-90 labeled anti-Tac. There is no teaching or suggestion as to the amount of anti-Tac provided to patients, nor is there any teaching or suggestion that the amount of the conjugate administered is related to the soluble levels of IL-2R. An anticipatory reference must teach every element of a claim, either expressly or under the doctrine of inherency. However, as stated by the Federal Circuit in *Continental Can Co. USA, Inc. v. Monsanto Co.* (948 F.2d 1264, 1268 (Fed. Cir. 1991)),

> [t]o serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, *and that it would be so recognized by persons of ordinary skill.* ... [Thus], this modest flexibility in the rule that 'anticipation' requires that every element of the claims appear in a single reference accommodates situations where the common knowledge of technologists is not recorded in the reference; that is, *where the technological facts are*

known to those in the field of the invention, albeit not known to judges.

Therefore, it is the Federal Circuit's position that for a teaching to be disclosed under the doctrine of inherency, the missing matter must be "recognized by persons of ordinary skill". In stark contrast, the claimed method is not only NOT taught or suggested by Waldmann 1993, but one skilled in the art would not have known how to determine the dosages of yttrium-90 conjugated anti-Tac based upon this reference, or any prior art reference cited by the Examiner. Thus, Waldmann does not teach expressly, or under the doctrine of inherency, the claimed method.

The Examiner's Error Regarding Obviousness

The Examiner has also erred in asserting the claimed invention is obvious over Waldmann 1993 as evidenced by Waldmann 1995 and Vriesendorp. Obviousness requires that the differences between the claimed subject matter and the prior art are such that "the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. §103; *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 958 (Fed. Cir. 1986). There is nothing in the Waldmann 1993 reference taken alone or in view of Vriesendorp (Waldmann 1995 is not prior art under US Statute) that would lead the skilled artisan to select a yttrium-90 anti-Tac at the dosage ranges claimed for patients having a given soluble IL-2R level.

The skilled artisan could not determine the correct dose of ^{90}Y-conjugated anti-Tac based upon the Waldmann 1993 article. Also, the reference does not teach or suggest the use of low doses of anti-Tac; i.e. less than 20 mg per

dose. The Waldmann reference does not teach or suggest a ^{90}Y-conjugated anti-Tac can be used at the claimed dosage ranges having the claimed levels of radioactivity. These missing elements could not be determined by one skilled in the art based upon the Waldmann 1993 article. In fact, the skilled artisan reading the Waldmann article would conclude that there is no correlation between sIL-2R levels and unlabeled anti-Tac dosage, let alone ^{90}Y-conjugated anti-Tac. Thus, the subject matter of claim 27 as a whole was not made obvious by the Waldmann article to the skilled artisan at the time of the invention.

As discussed above, Waldmann 1993 describes a clinical study of ATL patients treated with UNLABELED anti-Tac. These patients had soluble IL-2R levels ranging from 920 to 230,370 U/mL, yet all of the patients were given uniform amounts of unlabeled anti-Tac. Thus, there is no basis in Waldmann 1993, taken alone or in combination with Vriesendorp that would lead the skilled artisan to a reasonable expectation of success using a labeled anti-Tac wherein the dosage is correlated with the soluble IL-2R levels in the patient. The Examiner's view that success would be inherent is flawed. To preclude patentability under 35 U.S.C. §103, there must be some predictability of success in any attempt to combine elements of reference processes. The view that success would have been "inherent" cannot substitute for a showing of reasonable expectation of success. *In re Rinehart*, 531 F.2d 1048, 1054 (C.C.P.A. 1976).

The Examiner takes the position that "one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed

invention" and that it would have been "readily apparent to one of ordinary skill in the art at the time the invention was made". From the scientific view, the Examiner's statements are reckless. How could it be readily apparent to one of ordinary skill in the art that 5-15 mCi ^{90}Y conjugated to 20 mg of anti-Tac should be administered to a patient *if and only if* the patient has soluble IL-2R levels of over 50,000 U/ml from a reference that does not make any correlation to soluble IL-2R levels and does not teach the use of labeled anti-Tac in any particular amount? How could one expect to make this leap with "a reasonable expectation of success"? This invention is in the biomedical arts, which like the chemical and biotechnology arts is highly unpredictable in its very nature. Extensive patient studies are used to arrive at dosing schemes. The medical practice would not reach the claimed invention from reading the Waldmann 1993 reference.

In addition, the Examiner repeatedly points out that "for examination purposes given the claimed recitation; all that is required of the prior art is to provide a dosage of mCi and an amount of ^{90}Y-conjugated anti-Tac to a patient with one of the soluble IL-2R levels." *See, e.g.* page 4, 6th paragraph, and page 7, first paragraph of Paper No. 29. Appellant respectfully disagrees with this position. However, *assuming arguendo* this position is appropriate, the Examiner has not pointed to a single such scenario in the cited art. That is, the cited prior art does not show any one patient having soluble IL-2R levels of less than 2000 units/ml being given 2 mg total ^{90}Y-conjugated anti-Tac, or a patient having soluble IL-2R levels of 2,000-10,000 units/ml being given 5 mg total ^{90}Y-conjugated anti-Tac, or a patient

having soluble IL-2R levels of 10,000-50,000 units/ml being given 10 mg total ^{90}Y-conjugated anti-Tac or a patient having soluble IL-2R levels of greater than 50,000 units/ml being given 20 mg total ^{90}Y-conjugated anti-Tac. Thus, the Examiner has not made a *prima facie* showing of anticipation and/or obviousness against claim 27. Accordingly, for the above reasons, Appellant respectfully requests that the Board order that the final rejection of Claim 27 be withdrawn, that Appellant's Claim 27 be confirmed as patentable, and that a certificate be issued confirming patentability of Claim 27.

Issue 2: ***Is claim 27 unpatentable under 35 U.S.C. §103(a) as being obvious over Waldmann, 1993 and/or Waldmann (Important Adv. Oncol., 1994:892) ("the IAO reference") and/or Waldmann (Leukemia 7, Suppl 2:S151-S156) ("the Leukemia reference") and/or Waldmann (Ann. Oncol. 5:13-17, 1994) ("the Ann.Oncol. reference") in view of Vriesendorp and Rubin (Ann. Int. Med. 113:619-627, 1990) ("Rubin")?***

A. The Cited Art

1. The IAO Reference

The IAO reference is a review article describing anti-Tac treatment of T-cell lymphoma. The article first discusses the structure and function of the IL-2 receptor and diseases associated with elevated levels of the receptor. Next, the article describes therapies for treating these diseases using unlabeled anti-Tac. Humanization of the anti-Tac and use of bifunctional antibodies are discussed by Waldmann in the IAO reference. Finally, anti-Tac conjugates are described. Pseudomonas exotoxin conjugates as well as radionuclide conjugates are discussed in a general fashion. In describing the use of ^{90}Y-conjugated anti-Tac, the following

passage appears:

> To date, 17 patients with ATL have been treated with a total of 53 doses of ^{90}Y-labeled murine anti-Tac, initially in a phase I dose escalation trial and subsequently in a phase II trial involving 10 **μCi** of ^{90}Y-labeled anti-Tac per patient dose (Waldmann, unpublished observation). Patients undergoing a partial or complete remission were permitted to receive up to 8 additional doses of ^{90}Y-labeled anti-Tac with a minimum of 6 weeks between courses. At the 5- to 15-**μCi** doses used, 11 of the 17 patients responded to ^{90}Y-anti-Tac ...
> *IAO reference at 138 (emphasis added).*

Note that the described amount of yttrium-90 in the IAO article is 3 orders of magnitude below that claimed (i.e. μCi versus mCi).

No specific dosage amounts for therapy are provided in the IAO reference.

2. *The Ann. Oncol. Article*

This is a review article which generally discusses the use of lymphokine receptors as a target for immunotherapy for lymphomas. The focus of the article is directed to the IL-2 receptor. Anti-Tac therapies are identified, but no specific doses are taught or suggested. The article also discusses the use of antibody conjugates, and in particular, the use of antibodies armed with cytotoxic agents. Nowhere in this review article are any anti-Tac dosages taught or suggested.

3. *The Leukemia Article*

This article memorializes a lecture given by Dr. Waldmann and relates to targeting the IL-2 receptor for treating human T-cell lymphotrophic virus I (HTLV-I)-associated leukemia/lymphoma or ATL. The article describes IL-2R structure and

function and the use of anti-Tac as treatment for ATL. Similar to the other review articles discussed above, this reference describes humanized anti-Tac and the use of radionuclide-conjugated anti-Tac. As with the other review articles, no specific dosage amounts for therapy are provided.

B. The Examiner's Rejection

Claims 27 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Waldmann 1993 and/or the IAO reference and/or the *Leukemia* article and/or the *Ann. Oncol.* article in view of Vriesendorp and Rubin. In particular, the Examiner contends that the cited articles describe administration of 5 - 15 mCi doses of ^{90}Y anti-Tac antibody to patients resulting in either partial or complete remissions. The Examiner concedes that the Waldmann teachings (i.e. Waldmann 1993, the IAO reference, the *Leukemia* article and the *Ann.Oncol.* article) differ from the claimed method by not disclosing the particular mg amount of the 5-15 mCi doses of ^{90}Y anti-Tac antibody. The Examiner relies upon Vrisendorp as it describes that the specific activity for yttrium-90 labeled antibodies is 5 - 50 mCi per mg protein. Rubin describes that soluble IL-2 receptors are measured in a number of human diseases, according to the Examiner.

The Examiner's position is summarized by the following passage, taken from his final Official Action:

> [I]t would have been obvious to one of ordinary skill in the art to select for appropriate amounts of radiolabeled anti-Tac antibody (e.g. mg and mCi of anti-Tac antibodies) in

> vivo to achieve therapeutic efficacy in the face of soluble IL-2 receptors in patients. It would have been recognized that there would have been a range of therapeutic doses since differences in the nature of diseases as well as individual patients were known and expected in the art at the time the invention was made.

C. Appellant's Response

As described above and conceded to by the Examiner, the Waldmann articles simply mention 5-15 mCi doses of ^{90}Y-labeled anti-Tac antibodies. There is no teaching or suggestion of the amount of antibody in milligrams the radiation dosage is contained in, nor is there any suggestion of the sIL-2 receptor levels of the patients. More importantly, there is no suggestion of a relationship between the radiation dosage, the amount of antibody in mg, and the level of sIL-2. Finally, there is no teaching or suggestion of the correlation between dosage and soluble IL-2R levels. Combining Vriesendorp and Rubin to the Waldmann articles does not cure the deficiencies of the Waldmann articles.

The Examiner points to Waldmann 1993 as an example of the teachings he relies on in concluding the claimed invention was obvious. The Examiner asserts that Waldmann (1993) describes the use of 20 mg of unlabeled anti-Tac, describes conjugating cytotoxic agents to anti-Tac, and describes a 2-17 mg anti-Tac requirement to achieve circulating bioavailable levels in a patient.

In fact, Waldmann 1993 describes the results of a study which used unlabeled anti-Tac in patients having a broad range of sIL-2R levels (i.e. from 920-230,370 U/ml). The statement regarding the use of 2-17 mg of anti-Tac relates to a parallel study carried out to determine the minimum amount of anti-Tac necessary to

detect bioavailable circulating anti-Tac. This level is quite different than the amount of anti-Tac necessary (and used in Waldmann 1993) *to saturate sIL-2R* and thus treat the disease. Throughout the Waldmann 1993 reference, the researchers use unlabeled antibody and as the study progresses choose higher doses (i.e. 50 mg) for treatment. If the use of lower doses had been as obvious as the Examiner asserts, why did Waldmann select the higher doses? Reading the reference as a whole, the skilled artisan would conclude that the higher doses were necessary to achieve therapeutic results. Thus, in contrast to the Examiner's position, there is no motivation in the cited Waldmann references to select the lower doses for therapeutic treatment methods. As discussed above, the lower doses (i.e. 2-17 mg) described in Waldmann 1993 relate to the determination of minimum amounts of anti-Tac necessary to have "circulating bioavailable" anti-Tac. For therapeutic purposes however, Waldmann 1993 teaches that "receptor saturation" is needed, therefore necessitating the higher dosage requirements.

Vriesendorp describes the use of radiolabeled antiferritin antibodies for radioimmunoglobulin therapy for refractory Hodgkin's disease patients. The conjugation methods described by Vriesendorp produced antibodies with specific activities of "2-5 mCi per mg protein for indium-111 labeled antibodies, and between 5-40 mCi per mg protein for yttrium-90 labeled antibodies." Vriesendorp does not indicate which of the methods were used to chelate yttrium, nor is there any indication as to why there is such a broad range of radioactivity per mg of antibody.

The present invention does not use an antiferritin antibody, nor does it

necessarily use the same method of yttrium conjugation described by Vriesendorp. It is not possible to extrapolate from Vriesendorp to determine the radioactivity per mg of antibody in Waldmann. One skilled in the art recognized that specific activity was not a universally applicable number arrived at by correlation to other antibodies conjugated to radionuclides by other methods. One skilled in the art would not read Vriesendorp which labeled antiferritin antibodies with yttrium-90, and conclude that anti-Tac labeled with yttrium-90, (or any other antibody labeled with yttrium-90) regardless of the method of conjugation, must have the same specific activity. In fact, the instant specification makes clear that the concentration of labeled anti-Tac antibody administered to a patient is carefully controlled by diluting the labeled antibody with unlabeled antibody to control the total quantity of antibody administered. *See* Spec. at page 42, lines 14-18.

The Examiner also asserts that the cited Waldmann references "teach [that] elevated levels of the soluble IL-2R was associated with neoplastic disorders" and that Rubin reviews that "soluble IL-2 receptors were measured in a number of human diseases, including the malignancies encompassed by the claimed invention." From this, the Examiner concludes that "the soluble IL-2 receptor levels encompassed by the claimed methods were expected levels of malignant patients at the time the invention was made." While it is true that levels of IL-2R for patients with malignancies were known (*see* e.g. Table 1 of Waldmann 1993), none of the cited prior art made any correlation between these sIL-2R levels and a particular dosage of ^{90}Y conjugated anti-Tac. Thus, the skilled artisan could not have

recognized such a correlation from the cited art. Indeed, the Waldmann 1993 reference would have led the skilled artisan to conclude that there was NO correlation between sIL-2R levels and anti-Tac dosage, because despite the broad range of patient sIL-2R levels, the patients received a uniform dose of anti-Tac.

The combination of the Waldmann articles in view of Vriesendorp and Rubin does not teach or suggest the use of yttrium-90 conjugated anti-Tac in any dosage within the ranges claimed for a given level of soluble IL-2R. Neither Vriesendorp nor Rubin provide the missing teaching that 2-20 mg of anti-Tac should be used. One skilled in the art would not conclude from the Waldmann articles, Vriesendorp and Rubin that 5-15 mCi of yttrium-90 conjugated to 2-20 mg anti-Tac should be administered to patients with any particular soluble IL-2R level. There is no correlation between the labeling of yttrium-90 to a antiferritin antibody to yttrium-90 labeling of a Tac antibody to soluble IL-2 receptor levels. In sum, the cited prior art does not teach or suggest (1) a correlation between a patient's soluble IL-2 receptor levels and a particular dose of ^{90}Y-conjugated anti-Tac; or (2) the use of a ^{90}Y-conjugated Tac antibody provided at a specific activity of 5-15 mCi ^{90}Y and 2-20 mg of Tac antibody. Thus, this combination of prior art does not render obvious claim 27. Accordingly, for the above reasons, Appellant respectfully requests that the Board order that the final rejection of Claim 27 be withdrawn, that Appellant's Claim 27 be confirmed as patentable, and that a certificate be issued confirming patentability of Claim 27.

IX. CONCLUSION

Appellant's invention as recited in Claim 27 is patentable over the cited art. The Examiner's final rejection of Appellant's Claim 27 under 35 U.S.C. § 102(b) and/or 103 is in error, and therefore must be withdrawn. Accordingly, Appellant respectfully requests that the Board order that the final rejection of Claim 27 be withdrawn, that Appellant's Claim 27 be confirmed as patentable, and that a certificate be issued confirming patentability of Claim 27.

Respectfully submitted,

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APPENDIX

27. A method of reducing levels of Tac-positive cells in patients with elevated levels of Tac-positive cells comprising the steps of,

a) determining a dosage, said dosage comprising 5-15 mCi ^{90}Y-conjugated anti-Tac in a total amount of 2-20 mg anti-Tac, wherein the dose is 2 mg total anti-Tac if said patient has sIL-2R levels of less than 2,000 units/ml, the dose is 5 mg total anti-Tac if said patient has sIL-2R levels of 2,000 - 10,000 units/ml, the dose is 10 mg of total anti-Tac if the patient has sIL-2R levels of 10,000 - 50,000 units/ml, and the dose is 20 mg of total anti-Tac if said patient has sIL-2R levels of greater than 50,000 units/ml; and

b) administering said dosage to said patient to eliminate disease-associated Tac-positive cells.